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JOURNAL OF HEPATOLOGY

STARTVerso1: A randomized trial of faldaprevir plus pegylated interferon/ribavirin for chronic HCV genotype-1 infection☆

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Background & Aims: The efficacy and tolerability of faldaprevir, a potent hepatitis C virus (HCV) NS3/4A protease inhibitor, plus peginterferon (PegIFN) and ribavirin (RBV) was assessed in a double-blind, placebo-controlled phase 3 study of treatment-naïve patients with HCV genotype-1 infection.

Methods: Patients were randomly assigned (1:2:2) to PegIFN/RBV plus: placebo (arm 1, n = 132) for 24 weeks; faldaprevir (120 mg, once daily) for 12 or 24 weeks (arm 2, n = 259); or faldaprevir (240 mg, once daily) for 12 weeks (arm 3, n = 261). In arms 2 and 3, patients with early treatment success (HCV-RNA <25 IU/ml at week 4 and undetectable at week 8) stopped all treatment at week 24. Other patients received PegIFN/RBV until week 48 unless they met futility criteria. The primary endpoint was sustained virologic response 12 weeks post-treatment (SVR12).

Results: SVR12 was achieved by 52%, 79%, and 80% of patients in arms 1, 2, and 3, respectively (estimated difference for arms 2 and 3 *vs.* arm 1: 27%, 95% confidence interval 17%–36%; and 29%, 95% confidence interval, 19%–38%, respectively; p <0.0001 for both). Early treatment success was achieved by 87% (arm 2) and 89% (arm 3) of patients, of whom 86% and 89% achieved SVR12. Adverse event rates were similar among groups; few adverse events led to discontinuation of all regimen components.

Conclusions: Faldaprevir plus PegIFN/RBV significantly increased SVR12, compared with PegIFN/RBV, in treatment-naïve patients with HCV genotype-1 infection. No differences were seen in responses of patients given faldaprevir once daily at 120 or 240 mg.

Keywords: NS3/4A protease inhibitor; SVR12; Early treatment success; DAA; Clinical trial; Phase 3.

Received 5 August 2014; received in revised form 5 December 2014; accepted 19 December 2014; available online 2 January 2015

ClinicalTrials.gov registration number: NCT01343888.

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Abbreviations: HCV, hepatitis C virus; PI, protease inhibitor; PegIFN, peginterferon; RBV, ribavirin; SVR, sustained virologic response; DDI, drug–drug interaction; BID, twice daily; ETS, early treatment success; TD, target detected; TND, target not detected; EVR, early virologic response; ETR, end of treatment response; RVR, rapid virologic response; cEVR, complete early virologic response; PPV, positive predictive value; NPV, negative predictive value; AE, adverse event; DAIDS, Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events; ITT, intention-to-treat; RAV, resistance-associated variant; GI, gastrointestinal; ULN, upper limit of normal.

Introduction

The introduction of the hepatitis C virus (HCV) NS3/4A protease inhibitors (PI) telaprevir and boceprevir represented a major advance in the treatment of chronic HCV genotype-1. Telaprevir or boceprevir with peginterferon (PegIFN) and ribavirin (RBV) resulted in a sustained virologic response (SVR) in 63%–75% of treatment-naïve patients, compared with 38%–44% with PegIFN and RBV alone [1–4]. However, these drugs have limitations, including serious skin reactions with telaprevir [5], and an increased incidence of anemia, compared with PegIFN and RBV alone, with both telaprevir and boceprevir [1–4]. Furthermore, both drugs also display a wide range of drug–drug interactions (DDIs), have a high pill burden, and require twice daily (BID) or three times daily dosing [5–9].

Faldaprevir (BI 201335) is a potent HCV NS3/4A PI administered once daily [10–12]. Four phase 2 studies evaluated the efficacy and safety of faldaprevir with PegIFN alfa-2a plus RBV [13–16]. In genotype-1 treatment-naïve patients, SVR rates of up to 84% were achieved compared with 56% for placebo plus PegIFN and RBV [13]. In addition, SVR rates were similar with faldaprevir 120 mg for 12 or 24 weeks [16]. The addition of faldaprevir to PegIFN and RBV was not associated with an increased incidence of anemia compared with PegIFN and RBV alone [13,16] and there have been no reports of potentially life-threatening cutaneous adverse reactions in phase 2 studies [13,14,16]. Studies of faldaprevir and antiretrovirals have shown a lower potential for DDIs than first-wave PIs [17].

STARTVerso1 was a phase 3 study designed to assess the efficacy and safety of faldaprevir with PegIFN and RBV in treatment-naïve patients with chronic HCV genotype-1 infection.

Patients and methods

Patients

Patients were recruited from nine European countries and Japan. Eligible patients were treatment-naïve, aged 18–70 years (Europe), or 20–70 years (Japan), with chronic HCV genotype-1 infection diagnosed by positive anti-HCV antibodies and HCV RNA ⩾1000 IU/ml at screening plus a positive antibody or HCV RNA test more than 6 months before screening, or a liver biopsy consistent with chronic HCV infection.

Patients with compensated liver disease, including cirrhosis, were eligible for inclusion. All patients had a liver biopsy within 3 years or had a FibroScan® within 6 months of randomization to determine fibrosis stage. For patients without a liver biopsy, fibrosis stage was determined by FibroScan® results using a cut-off value of 9.5 kPa to indicate fibrosis stage ⩾F3 (<9.5 kPa F0–F2; ⩾9.5 kPa F3–F4), consistent with evaluations of the use of FibroScan® in chronic HCV [18,19]; however, there are no reliable cut-offs in the literature for distinguishing <F3 from ⩾F3. The FibroScan® threshold for cirrhosis was ⩾13 kPa, based on the results of a meta-analysis by Friedrich-Rust *et al.*, and consistent with results of other studies [20,21]. Main exclusion criteria included mixed-genotype HCV; HIV or hepatitis B co-infection; decompensated liver disease; and contraindications to PegIFN or RBV. Asian patients were limited to 20% of the total population.

Study design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group phase 3 study (Fig. 1). Patients were randomized 1:2:2 to arm 1, 2, or 3. Patients in arm 1 received placebo plus PegIFN and RBV for 24 weeks, then PegIFN and RBV for 24 weeks. Patients in arm 2 received faldaprevir 120 mg once daily plus PegIFN and RBV. Those with early treatment success (ETS, HCV RNA <25 IU/ml target detected [TD] or target not detected [TND] at week 4 and <25 IU/ml TND at week 8) stopped faldaprevir at week 12 and received placebo plus PegIFN and RBV for a further 12 weeks. Patients without ETS received faldaprevir plus PegIFN and RBV for 24 weeks, then PegIFN and RBV for a further 24 weeks. In arm 3, all patients received faldaprevir 240 mg once daily plus PegIFN and RBV for 12 weeks followed by placebo plus PegIFN and RBV to week 24, and either stopped treatment (ETS) or continued PegIFN and RBV to week 48 (no ETS) (Fig. 1). A single loading dose of faldaprevir was administered on day 1 (arm 2 = 240 mg; arm 3 = 480 mg). All study medication was stopped in the event of virologic breakthrough at or after week 4 (increase in HCV RNA ⩾1 $\log_{10}$ from nadir or ⩾25 IU/ml after an initial decrease to <25 IU/ml), lack of early virologic response (EVR; decrease in HCV RNA ⩾2 $\log_{10}$ from baseline at week 12), or lack of virologic response (detectable HCV RNA at week 24).

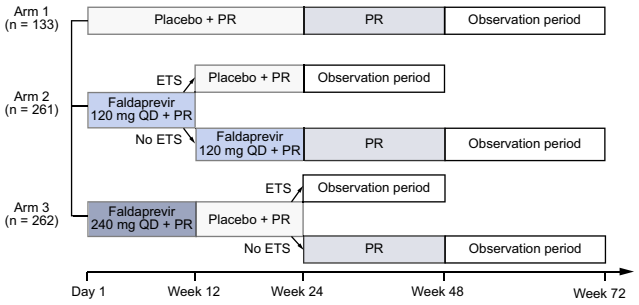

Fig. 1. STARTVerso1 study design. ETS, early treatment success (HCV RNA <25 IU/ml at week 4 and target not detected at week 8); PR, PegIFN alfa-2a and RBV.

PegIFN (alfa-2a) was administered subcutaneously at 180 μg once weekly. RBV was administered orally at a total dose of 1000 or 1200 mg (for bodyweight <75 kg or ⩾75 kg, respectively) daily in two divided doses, except in Japan where the total dose was 600, 800, or 1200 mg (for bodyweight ⩽60 kg, >60–⩽80 kg, or >80 kg, respectively) daily in two divided doses according to the local label. Both faldaprevir and RBV were given with food, a requirement of RBV but not faldaprevir administration. Dose reductions were permitted for PegIFN and RBV, and brief dose interruptions were permitted for all three drugs, but only if medically necessary and following discussion with the clinical monitor. Faldaprevir monotherapy was not permitted. Treatment compliance was monitored using pill counts and syringe counts at each visit.

Concomitant use of the following drugs was not permitted: immunomodulators (including chronic use of systemic corticosteroids); systemic antiviral agents (except for treatment of mild, localized, recurrent herpes simplex, or influenza); and medications that could cause phototoxicity (except RBV). Concomitant treatment with methadone or buprenorphine was excluded, and the use of substrates of P-glycoprotein, UGT1A1, CYP3A4, or CYP2C9 with a narrow therapeutic window were discouraged.

Study documentation, including protocol amendments, was approved by the appropriate institutional review board and the study was carried out in accordance with the Declaration of Helsinki and International Conference on Harmonisation guidelines. All patients provided written informed consent. An independent data monitoring committee reviewed the efficacy and safety data at regular intervals. All authors had access to the study data and reviewed and approved the final manuscript.

Randomization and blinding

Randomization was carried out using an interactive voice response system, and was stratified according to race (Black, Asian, other) and HCV genotype (genotype-1a, genotype-1b, other). Investigators, sponsor, and patients were blinded to treatment group allocation through the use of matching placebo capsules. HCV RNA results were blinded up to week 8.

Virologic endpoints

The primary endpoint was SVR (HCV RNA <25 IU/ml TND) 12 weeks after completion of therapy (SVR12). Secondary endpoints were ETS, and ALT and AST normalization. Other endpoints were rapid virologic response (RVR, HCV RNA <25 IU/ml TD or TND at week 4); complete EVR (cEVR, HCV RNA <25 IU/ml TND at week 12); and end of treatment response (ETR, HCV RNA <25 IU/ml TND at end of treatment).

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HCV RNA levels were measured using the quantitative Roche COBAS® Taqman HCV/HPS assay version 2 (lower limit of quantification 25 IU/ml; limit of detection 9–20 IU/ml). The primary endpoint was changed from SVR24 to SVR12 by a protocol amendment, consistent with evidence of concordance between SVR12 and SVR24 [22].

Resistance monitoring

Samples were obtained for viral sequencing at baseline and at study visits. Baseline samples and samples from patients who did not achieve SVR12 were analyzed. HCV RNA was amplified by reverse transcriptase polymerase chain reaction and population sequencing performed on the NS3 or NS3/4A regions (Big Dye Terminator and an ABI 3730XL Genetic Analyser [Applied Biosystems]).

Safety assessments

Safety was assessed by monitoring adverse events (AEs) and laboratory parameters throughout the trial and 28 days post-treatment. Patients with persisting AEs were monitored until the event resolved. With the exception of photosensitivity, AEs were graded as mild (Grade 1), moderate (Grade 2), severe (Grade 3), or potentially life-threatening (Grade 4) using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS) [23]. Photosensitivity was graded as mild, moderate, or severe according to predefined criteria (see Supplementary Tables). A rash management plan was used to reduce the progression of rash intensity and minimize the risk of photosensitivity. Patients were provided with sun protection and were instructed to protect eyes and skin from sun- or UV-light exposure using a sun protection factor $\geqslant$30 providing UVA and UVB coverage.

Statistical analysis

Based on a sample size of 125 patients in the placebo arm and 250 patients in each of the faldaprevir arms, the study was anticipated to have a power of 96% to detect, with alpha = 0.05 (2-sided), an effect size of 20% for the primary endpoint, assuming an SVR12 of 50% in the placebo arm.

The primary efficacy analyses were based on the intention-to-treat (ITT) population (all randomized patients who received at least one dose of study medication). The safety analysis set included all patients who received at least one dose of study medication regardless of randomization.

The proportion of patients with SVR12 was compared pairwise using the Cochran–Mantel–Haenszel test, stratified by race and genotype-1 subtype. A hierarchical testing strategy was pre-specified, with the test for the lower dose only interpreted if the higher dose was statistically significant. Thus, no alpha adjustment was necessary. ETS was summarized descriptively (numbers and proportions of patients reaching the endpoint in each arm). All other efficacy and safety data were summarized descriptively.

Positive and negative predictive values (PPVs and NPVs) for SVR12 based on different HCV RNA thresholds (1000 IU/ml, 100 IU/ml, 25 IU/ml, and detectable) were calculated for all faldaprevir-treated patients with HCV RNA measurements at weeks 2, 4, 8, and 12 on treatment.

Results

Patients

Patients were enrolled from April 14 through to November 11, 2011 at 102 sites from 10 European countries and Japan; the last patient completed follow-up on February 12, 2013. All patients were enrolled prior to the availability of telaprevir or boceprevir in Europe and Japan. Of 778 patients screened, 656 were randomized and 652 were treated with placebo (n = 132), faldaprevir 120 mg (n = 259), or faldaprevir 240 mg (n = 261) (Fig. 2). The baseline demographic characteristics were similar across the arms (Table 1). Liver biopsies were available for 312/652 patients—115 (44%), 131 (51%), and 66 (50%) in the faldaprevir 120 mg, faldaprevir 240 mg, and placebo arms, respectively. FibroScan® scores were available for 353/652 patients—148

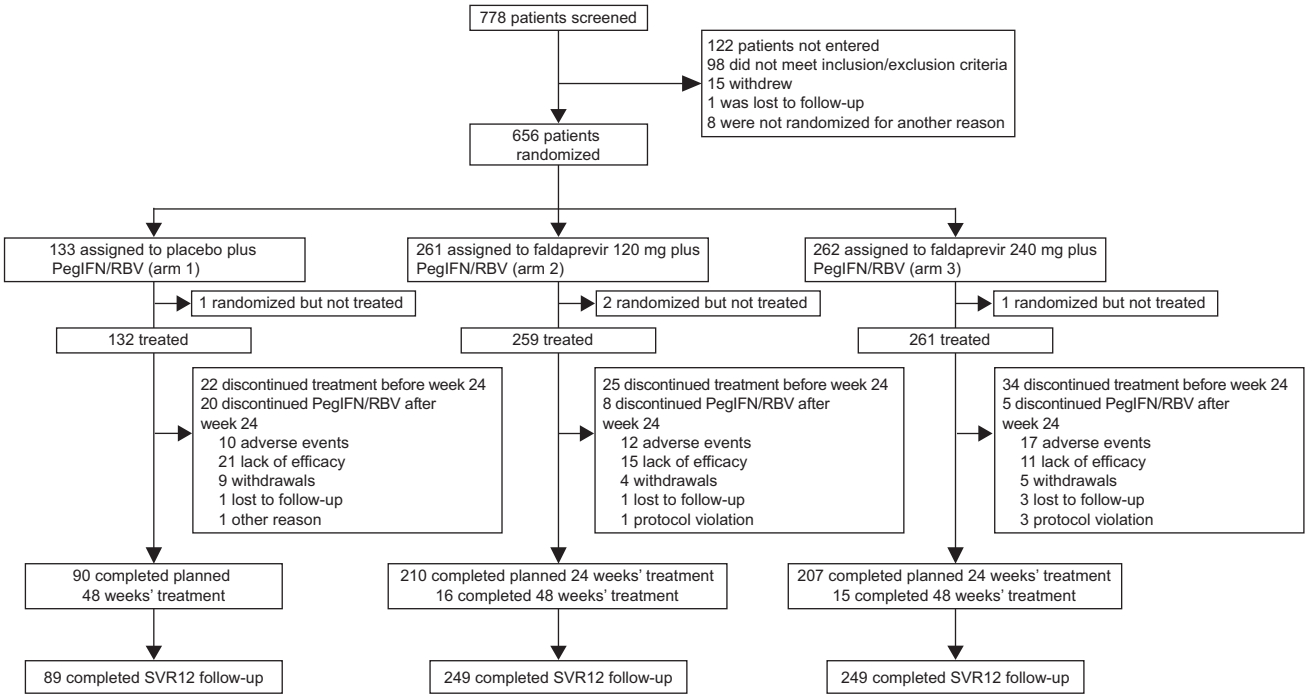

Fig. 2. Randomization, treatment, and follow-up of study patients. Patients who met a stopping rule were classified as having a lack of efficacy (virologic breakthrough at or after week 4; lack of early virologic response; or lack of virologic response at end of treatment). Before week 8, the interactive voice response system informed investigators if patients had met criteria to stop treatment due to lack of efficacy. After week 8, lack of efficacy was determined by investigators based on HCV RNA results.

Table 1. Baseline demographics and clinical characteristics.

	Placebo + PegIFN and RBV (N = 132)	Faldaprevir 120 mg + PegIFN and RBV (N = 259)	Faldaprevir 240 mg + PegIFN and RBV (N = 261)
Male, n (%)	75 (57)	121 (47)	146 (56)
Race, n (%)			
White	103 (78)	203 (78)	205 (79)
Asian*	27 (20)	52 (20)	51 (20)
Black/AA	2 (2)	3 (1)	4 (2)
Other†	0	1 (<1)	1 (<1)
Region, n (%)			
Europe	108 (82)	207 (80)	211 (81)
Asia	24 (18)	52 (20)	50 (19)
Mean age, years (SD)	46.6 (12.5)	47.9 (11.4)	48.3 (11.9)
Mean BMI, kg/m^2 (SD)	24.6 (4.3)	24.9 (4.2)	25.2 (4.6)
HCV genotype-1 subtype, n (%)‡			
1a	45 (34)	87 (34)	90 (34)
1b	86 (65)	171 (66)	171 (66)
Mean baseline HCV RNA, log$_{10}$ IU/ml (SD)	6.3 (0.7)	6.3 (0.7)	6.2 (0.8)
Baseline HCV RNA ≥800,000 IU/ml, n (%)	101 (77)	201 (78)	185 (71)
IL28B (rs12979860), n (%)			
CC	46 (35)	107 (41)	101 (39)
CT	68 (52)	122 (47)	126 (48)
TT	18 (14)	29 (11)	34 (13)
Fibrosis stage, n (%)§			
<F3	107 (81)	212 (82)	219 (84)
≥F3	25 (19)	45 (17)	42 (16)
Missing	0	2 (1)	0
Cirrhosis‖, n (%)	8 (6)	16 (6)	15 (6)
Mean ALT, IU/L (SD) [range]	75 (68) [15-360]	75 (69) [15-726]	72 (52) [13-325]
Elevated ALT, n (%)	84 (64)	169 (65)	177 (68)
Elevated AST, n (%)	65 (49)**	117 (45)	133 (51)

*Four Asian patients were enrolled outside Japan. †Includes American Indian/Alaskan Native, and Native Hawaiian/other Pacific Islander. ‡Two patients (one each in the placebo and faldaprevir 120 mg arms) were infected with HCV genotype-1, but subtyping was indeterminate. §Liver biopsies were available for 312/652 patients—115/259 (44%) in the faldaprevir 120 mg arm; 131/261 (51%) in the faldaprevir 240 mg arm; and 66/132 (50%) in the placebo arm. Fibroscan results were used to determine stage of fibrosis for patients without a liver biopsy (<F3 = <9.5 kPa, ⩾F3 = ⩾9.5 kPa) [18,19]. If a patient was indicated to have cirrhosis but had neither biopsy nor Fibroscan data, they were classified as having ⩾F3 fibrosis. ‖Cirrhosis was determined by the investigator based on Fibroscan, biopsy, and/or other clinical parameters. **One patient had missing AST data at baseline. Reference ranges: ALT 0–35 U/L, AST 0–35 U/L.

AA, African American; ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; SD, standard deviation.

(57%), 138 (53%), and 67 (51%) in the faldaprevir 120 mg, faldaprevir 240 mg, and placebo arms, respectively.

Efficacy

SVR12 rates were significantly higher for faldaprevir 120 mg or 240 mg compared with placebo (79% and 80% compared with 52%, respectively; Table 2A). The estimated differences in SVR12 of faldaprevir *vs.* placebo were 27% (95% CI: 17–36) for faldaprevir 120 mg (p <0.0001) and 29% (95% CI: 19–38) for faldaprevir 240 mg (p <0.0001). The higher SVR12 rates with faldaprevir compared with placebo were also observed in subgroup analyses. SVR12 rates were similar for both doses of faldaprevir among all subgroups analyzed (Table 2B; Supplementary Fig. 1). However, the number of patients in the cirrhotic subgroup was small.

Overall, 87% and 89% of patients in the faldaprevir 120 mg and 240 mg arms, respectively, achieved ETS (Table 2A). Of those, 86% (faldaprevir 120 mg) and 89% (faldaprevir 240 mg) achieved SVR12. In both faldaprevir arms, among patients with ETS who completed 24 weeks of therapy, those with undetectable HCV RNA at week 4 had numerically higher rates of SVR12 than those with HCV RNA <25 IU/ml detectable at week 4 (faldaprevir 120 mg: 91% [155/171] *vs.* 77% [30/39]; faldaprevir 240 mg: 94% [167/178] *vs.* 72% [21/29]).

RVR was achieved by 91% and 93% of patients in the faldaprevir 120 mg and 240 mg arms, respectively, *vs.* 22% in the placebo group (Table 2A). cEVR was achieved by 90% of patients in both faldaprevir groups, *vs.* 46% in the placebo group. Among faldaprevir-treated patients with RVR, 83% (faldaprevir 120 mg) and 86% (faldaprevir 240 mg) achieved SVR12. Among those with cEVR, 85% (faldaprevir 120 mg) and 88% (faldaprevir 240 mg) achieved SVR12.

Based on pooled data from both faldaprevir arms, week 4 HCV RNA <25 IU/ml resulted in a PPV (for SVR12) of 85%; week 4 HCV RNA undetectable resulted in a PPV of 90% (Supplementary Table 1). The NPV of week 4 HCV RNA ⩾25 IU/ml was 87%, and

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Table 2. (A) Virologic and biochemical responses (ITT). (B) SVR12 by baseline subgroup (ITT).

A	Placebo + PegIFN and RBV (N = 132)	Faldaprevir 120 mg + PegIFN and RBV (N = 259)	Faldaprevir 240 mg + PegIFN and RBV (N = 261)
SVR12, n (%)	69 (52)	204 (79)	210 (80)
Estimate *vs.* placebo	-	26.7	28.6
95% CI		17.1, 36.3	19.0, 38.2
p value		<0.0001	<0.0001
ETS, n (%)	29 (22)	226 (87)	233 (89)
RVR, n (%)	29 (22)	236 (91)	243 (93)
cEVR, n (%)	60 (45)	233 (90)	236 (90)
ETR, n (%)	97 (73)	238 (92)	240 (92)
ALT normalization, n/N (%)*			
Baseline to EOT	51/84 (61)	113/169 (67)	137/177 (77)
Baseline to SVR12 visit	40/84 (48)	132/169 (78)	132/177 (75)
AST normalization, n/N (%)†			
Baseline to EOT	38/65 (58)	88/117 (75)	92/133 (69)
Baseline to SVR12 visit	29/65 (45)	100/117 (85)	93/133 (70)

B Subgroups n/N‡ (%)	Placebo + PegIFN and RBV (N = 132)	Faldaprevir 120 mg + PegIFN and RBV (N = 259)	Faldaprevir 240 mg + PegIFN and RBV (N = 261)
Race			
White	49/103 (48)	157/203 (77)	158/205 (77)
Asian	18/27 (67)	44/52 (85)	47/51 (92)
Black	2/2 (100)	2/3 (67)	4/4 (100)
IL28B (rs12979860)			
CC	29/46 (63)	96/107 (90)	96/101 (95)
CT	35/68 (51)	85/122 (70)	87/126 (69)
TT	5/18 (28)	22/29 (76)	27/34 (79)
HCV genotype-1 subtype			
1a	16/45 (36)	60/87 (69)	68/90 (76)
1b	52/86 (60)	143/171 (84)	142/171 (83)
Baseline HCV RNA			
<800,000 IU/ml	23/31 (74)	54/58 (93)	70/76 (92)
≥800,000 IU/ml	46/101 (46)	150/201 (75)	140/185 (76)
Cirrhosis			
Yes	3/8 (38)	9/16 (56)	6/15 (40)
No	66/124 (53)	195/243 (80)	204/246 (83)
Fibrosis stage			
≥F3	9/25 (36)	30/45 (67)	23/42 (55)
<F3	60/107 (56)	172/212 (81)	187/219 (85)

*In patients with elevated baseline ALT. †In patients with elevated baseline AST; one patient not included due to missing baseline AST data. ‡Denominator is the total number of patients in each subgroup.

ALT, alanine transaminase; AST, aspartate aminotransferase; cEVR, complete early virologic response (HCV RNA <25 IU/ml TND at week 12); EOT, end of treatment; ETR, end of treatment response (HCV RNA <25 IU/ml TND at end of all treatment); ETS, early treatment success (HCV RNA <25 IU/ml TD or TND at week 4 and <25 IU/ml TND at week 8); RVR, rapid virologic response (HCV RNA <25 IU/ml TD or TND at week 4); SVR12, sustained virologic response (HCV RNA <25 IU/ml TND) 12 weeks post-treatment.

of week 4 HCV RNA ⩾100 IU/ml was 100%. Using a threshold of week 4 HCV RNA detectable (either TD or HCV-RNA quantifiable) resulted in an NPV of 50%, while using a threshold of week 12 HCV RNA detectable (i.e., not achieving cEVR) resulted in an NPV of 95%.

Breakthrough occurred in 42 patients across all treatment arms, 23 of whom were infected with HCV genotype-1a (Table 3). Relapse occurred in 21%, 11%, and 9% of patients in the placebo, faldaprevir 120 mg, and faldaprevir 240 mg arms, respectively, and was more common in patients infected with genotype-1a (Table 3). One patient who received faldaprevir (0.2%) and 15 who received placebo (11%) had a null or partial response (Table 3). Of the 33 patients in the faldaprevir 120 mg arm without ETS who continued faldaprevir beyond week 12, 13 (39%) experienced viral breakthrough and 3 (9%) relapsed.

Of the faldaprevir-treated patients who failed to achieve SVR12, 87% (92/106) had an emergent resistance-associated variant (RAV). The most common emergent RAVs were R155K

Table 3. Patterns of treatment failure according to HCV genotype-1 subtype and treatment regimen.

	Placebo + PegIFN and RBV			Faldaprevir 120 mg + PegIFN and RBV			Faldaprevir 240 mg + PegIFN and RBV		
	GT-1a (n = 45)	GT-1b (n = 86)	Total (n = 132)	GT-1a (n = 87)	GT-1b (n = 171)	Total (n = 259)	GT-1a (n = 90)	GT-1b (n = 171)	Total (n = 261)
Virologic breakthrough, n (%)*	6 (13)	5 (6)	11 (8)	9 (10)	7 (4)	16 (6)	8 (9)	7 (4)	15 (6)
0-12 weeks	1 (2)	1 (1)	2 (2)	5 (6)	2 (1)	7 (3)	3 (3)	3 (2)	6 (2)
>12-24 weeks	3 (7)	1 (1)	4 (3)	2 (2)	4 (2)	6 (2)	3 (3)	3 (2)	6 (2)
>24 weeks	2 (4)	3 (4)	5 (4)	2 (2)	1 (1)	3 (1)	2 (2)	1 (1)	3 (1)
Null or partial response, n (%)†	8 (18)	7 (8)	15 (11)	1 (1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
Relapse, n/N (%)‡	8/25 (32)	10/60 (17)	18/86§ (21)	13/72 (18)	12/150 (8)	25/223§ (11)	10/73 (14)	10/139 (7)	20/212 (9)

*Confirmed increase in HCV RNA $\geqslant 1\ \log_{10}$ from nadir or $\geqslant 25$ IU/ml after an initial decrease to <25 IU/ml. †Null response, absence of HCV RNA drop by $\geqslant 2\ \log_{10}$ from baseline at week 12; partial response, $\geqslant 2\ \log_{10}$ decrease in HCV RNA from baseline at week 12, but not achieving HCV RNA <25 IU/ml TND by end of treatment. ‡HCV RNA >25 IU/ml during follow-up (up to SVR12 visit) after decrease to <25 IU/ml TND at end of treatment. Denominator is number of patients who completed planned treatment and had ETR. §One patient in the placebo arm and one patient in the faldaprevir 120 mg arm had undetermined HCV genotype-1 subtype. Both achieved ETR and neither relapsed. ETR, end of treatment response; GT, genotype; TND, target not detected.

Table 4. Summary of adverse events (AEs).

	Placebo + PegIFN and RBV (N = 132)	Faldaprevir 120 mg + PegIFN and RBV (N = 259)	Faldaprevir 240 mg + PegIFN and RBV (N = 261)
Any AE, n (%)	123 (93)	251 (97)	253 (97)
AEs leading to discontinuation of faldaprevir or placebo, n (%)	5 (4)	12 (5)	22 (8)
Of all study medications	5 (4)	10 (4)	14 (5)
Of faldaprevir or placebo only	0 (0)	2 (1)	8 (3)
AEs of at least moderate intensity, n (%)*	64 (48)	134 (52)	144 (55)
Anemia†	15 (11)	33 (13)	32 (12)
Neutropenia	15 (11)	24 (9)	17 (7)
Rash‡	8 (6)	21 (8)	23 (9)
Asthenia	4 (3)	15 (6)	13 (5)
Fatigue	5 (4)	14 (5)	14 (5)
Nausea	1 (1)	6 (2)	16 (6)
Vomiting	1 (1)	3 (1)	14 (5)
Bilirubin§	2 (2)	8 (3)	16 (6)
Any serious AE, n (%)‖	8 (6)	17 (7)	17 (7)
Nervous system disorders	0 (0)	5 (2)	0 (0)
Blood and lymphatic system disorders	1 (1)	1 (<1)	4 (2)
Gastrointestinal disorders	1 (1)	1 (<1)	3 (1)
Skin and subcutaneous tissue disorders	1 (1)	1 (<1)	3 (1)
General disorders and administration site conditions**	1 (1)	2 (1)	1 (<1)
Infections and infestations	1 (1)	1 (<1)	2 (1)

*$\geqslant$5% of patients in any treatment arm. Based on DAIDs grading system (Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening). †Includes all associated terms. ‡Includes all associated terms (maculopapular rash, macular rash, papular rash, erythematous rash, generalized rash, pruritic rash, drug eruption, toxic skin eruption, and urticaria). All patients with a moderate or severe rash or photosensitivity reaction were sent to a local expert dermatologist who reviewed the investigator's assessment. Data from these patients were additionally sent to a rash adjudication committee to ensure consistency of grading/categorizing and reporting across regions and sites. §Bilirubin-associated events, including jaundice. ‖$\geqslant$3 patients across treatment arms. **Includes the following: in the placebo arm, adverse drug reaction (1); in the faldaprevir 120 mg arm, asthenia (1) and chest pain (1); and in the faldaprevir 240 mg arm, pyrexia (1).

(31/48, 65%) and substitutions at D168 (43/44, 98%) in patients infected with genotype-1a and genotype-1b, respectively. None of the clinically relevant NS3 polymorphisms [24] detected at baseline (Supplementary Table 2), including the Q80K polymorphism (detected in 49/217 [23%] patients infected with genotype-1a) were associated with a reduction in SVR12. SVR12 was achieved by 99/139 (71%) faldaprevir-treated patients with wild-type Q80 *vs.* 25/33 (76%) with the Q80K polymorphism ($p = 0.67$; Supplementary Table 3).

Safety

AEs led to discontinuation of all study medications in 4% (5/132), 4% (10/259), and 5% (14/261) of patients treated with placebo, faldaprevir 120 mg, or faldaprevir 240 mg, respectively (Table 4). Discontinuation of faldaprevir only occurred in 1% (2/259) of patients in the 120 mg arm and 3% (8/261) of patients in the 240 mg arm. The most common AEs leading to

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discontinuation of faldaprevir were vomiting, nausea, jaundice, and rash (Supplementary Table 4).

Serious AEs were reported in 6%, 7%, and 7% of patients treated with placebo, faldaprevir 120 mg, or faldaprevir 240 mg, respectively. Mild AEs were reported by 52%, 48%, and 45%, moderate AEs by 33%, 31%, and 37%, and severe AEs by 14%, 19%, and 15% of patients treated with placebo, faldaprevir 120 mg, or faldaprevir 240 mg, respectively. Gastrointestinal (GI) AEs of at least moderate intensity were more frequent in patients who received faldaprevir 240 mg *vs.* 120 mg or placebo. The most frequently reported AEs of at least moderate intensity and serious AEs are summarized in Table 4.

Severe rash occurred in <1% of patients in each of the faldaprevir arms; no patient had life-threatening rash (Supplementary Table 5). Discontinuations of only faldaprevir or placebo due to rash occurred in two patients. Photosensitivity was infrequent (n = 15, 2%), with the majority of events occurring in the faldaprevir 240 mg arm (10/15). All but two events were classified as mild (Supplementary Table 5) and no discontinuations were reported due to photosensitivity.

Grade 3–4 abnormalities in white blood cells, platelets, neutrophils, and lymphocytes occurred with similar frequency across the treatment arms (Supplementary Table 6). There was no difference in hemoglobin levels between the treatment arms at any visit (Fig. 3). Up to week 24, proportions of patients with hemoglobin levels ⩽10 g/dl and ⩽8.5 g/dl were similar across treatment arms (Supplementary Table 6). The numbers of patients with hemoglobin reductions leading to RBV dose reduction were 32 (24%), 44 (17%), and 39 (15%) in the placebo, faldaprevir 120 mg, and 240 mg arms, respectively. Twenty-six patients received erythropoietin (4 [3%], 10 [4%], and 12 [5%], respectively). Among all patients with RBV dose reductions, SVR12 was 67% (21/32), 86% (50/58), and 84% (37/44) in the placebo, faldaprevir 120 mg, and faldaprevir 240 mg arms, respectively.

Total bilirubin levels more than 2.6 times the upper limit of normal (ULN) were more frequent in the faldaprevir arms. More patients had elevated bilirubin in the faldaprevir 240 mg arm than the 120 mg arm (Supplementary Table 6). Bilirubin elevations were characterized by predominantly unconjugated bilirubin, peaked around week 4, and returned to baseline levels in all patients after the end of faldaprevir treatment (Supplementary Fig. 2). Four patients in the faldaprevir 240 mg arm had DAIDS Grade 3 or 4 total bilirubin and direct bilirubin:total bilirubin ratio >0.5. None of these patients had concurrent elevations in ALT or AST >3×ULN, or any clinical signs of liver injury.

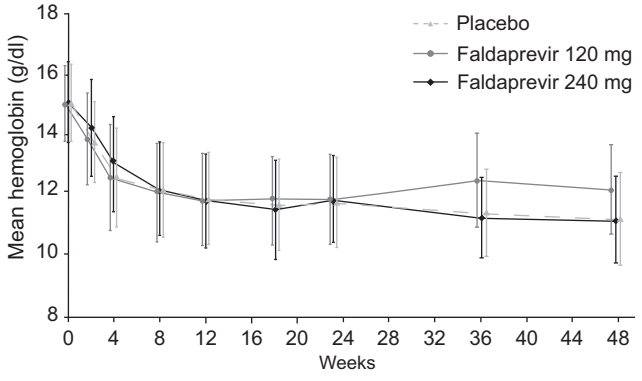

Fig. 3. Levels of hemoglobin over time.

Discussion

This study demonstrated that once-daily faldaprevir combined with PegIFN and RBV was significantly more effective than PegIFN and RBV alone in treatment-naïve patients with HCV genotype-1 infection. The majority of patients (88%) were eligible to receive 12 weeks of faldaprevir plus PegIFN and RBV and stop all treatment at week 24; of these patients, 88% achieved SVR12.

SVR12 rates were similar with the 120 mg and 240 mg doses of faldaprevir (79% and 80%, respectively), and significantly higher than with PegIFN and RBV alone (52%). An increase in SVR12 rates for faldaprevir over placebo was consistently observed across subgroups, although the study was not powered to assess statistical significance in the different subgroups and some subgroup comparisons are limited by small numbers. The increase in SVR12 for faldaprevir over placebo was higher in certain difficult-to-treat populations (HCV genotype-1a, high baseline HCV RNA, and *IL28B* non-CC) *vs.* the easier-to-treat subgroup.

Common baseline polymorphisms were not found to affect the efficacy of faldaprevir. The Q80K variant has been associated with reduced SVR12 in phase 3 studies of simeprevir [25,26]; however Q80K, present in 23% of genotype-1a-infected patients in this study, was not found to reduce SVR12 in faldaprevir-treated patients. As observed in phase 2 studies, RAVs encoding substitutions at positions R155 (genotype-1a) or D168 (genotype-1b) of HCV NS3 emerged in the majority of patients who did not achieve SVR12 [13,14].

While differences in patient populations and trial designs preclude direct comparison of these data with other studies, the 27% increase in SVR12 with faldaprevir plus PegIFN and RBV compared with PegIFN and RBV alone was similar to that reported in phase 3 trials of telaprevir (31% *vs.* placebo), boceprevir (28% *vs.* placebo), and simeprevir (30% *vs.* placebo) plus PegIFN and RBV in treatment-naïve patients with HCV genotype-1 [2,3,25,27]. More patients were able to stop treatment at week 24 with faldaprevir compared with telaprevir and boceprevir (88% *vs.* 58% and 47%, respectively), although that may be due in part to different HCV RNA criteria used for shortening treatment duration in the different trials [2,3]. Compared with simeprevir-treated patients, a similar proportion of faldaprevir-treated patients were able to stop at week 24 (88%) [25,27]. In all trials, patients who qualified for shortened treatment achieved a high SVR (>83%) [2,3,25,27].

Analysis of the predictive value of certain virologic endpoints suggests that a week 4 stopping rule for faldaprevir plus PegIFN and RBV should not use a threshold of detectable HCV RNA: 50% of patients who met this criterion went on to achieve SVR12 with continued treatment. A week 4 stopping rule using a threshold of ⩾25 IU/ml (NPV 87%) or ⩾100 IU/ml (NPV 100%) would more reliably stop treatment in patients unlikely to achieve a cure.

The higher (240 mg QD) dose of faldaprevir was associated with a minor increase in AEs compared with the lower (120 mg QD) dose or compared with PegIFN and RBV alone. The rate of treatment discontinuation was similar between the faldaprevir 120 mg and placebo arms, and only slightly higher in the

faldaprevir 240 mg arm. The addition of faldaprevir increased the rate of rash observed with PegIFN and RBV alone. However, the incidence of rash was similar with both faldaprevir doses and was mainly mild in intensity. Photosensitivity reactions were rare, supporting the use of sun protection during treatment with faldaprevir. Grade 2–4 GI events were more common in the faldaprevir 240 mg arm, and treatment discontinuation due to GI toxicities only occurred with this higher dose. These data indicate that faldaprevir may have a more favorable tolerability profile compared with telaprevir and boceprevir. While real-world data indicate that severe anemia is one of the most common AEs reported with first-wave PIs [28,29], faldaprevir did not increase the proportion of patients with hemoglobin levels below 10 g/dl or 8.5 g/dl compared with placebo.

As observed in phase 2 studies, faldaprevir was associated with a dose-dependent, transient, and benign elevation in predominantly unconjugated bilirubin [13,14]. Bilirubin levels returned to baseline after faldaprevir was stopped (Supplementary Fig. 2). Faldaprevir inhibits the bilirubin conjugation enzyme, UGT1A1, and to a lesser extent the bilirubin transporters, OATP1B1, and MRP2 [30]. Increases in bilirubin have also been observed with simeprevir; however, this is predominantly driven by inhibition of OATP1B1 and MRP2 [31].

A possible limitation to this study is that investigators were unblinded to HCV RNA results after week 8, which could have effectively unblinded the treatment allocation. In addition, the effects of faldaprevir on bilirubin could have been used to infer treatment allocation. However, few patients withdrew consent in this study, so the effect is likely to be negligible. Another potential limitation is the lack of baseline histology data on many patients due to the widespread use of FibroScan® in Europe. For patients without liver biopsies, we relied on FibroScan® scores to stage fibrosis; although the FibroScan® cut-off for cirrhosis is quite established, there is some disagreement about the optimal cut-off value for distinguishing <F3 from ⩾F3 fibrosis [18–21]. Nevertheless, there is no gold standard for defining fibrosis stage at all, since sampling error is a major problem with inadequate sized liver biopsies [32].

In addition to the results presented here, faldaprevir has shown efficacy as part of an interferon-based regimen for treatment-experienced patients (STARTVerso3) [33], and as part of an interferon-free regimen [34]. Regional differences in the cost of HCV therapies may lead to continued use of interferon-based regimens for the foreseeable future. Regimens that have been approved for treating genotype-1 infection include sofosbuvir plus PegIFN and RBV [35] and simeprevir plus PegIFN and RBV [25,27]. For patients ineligible for interferon, sofosbuvir plus simeprevir with or without RBV is recommended [36].

In conclusion, this phase 3 trial demonstrated that faldaprevir plus PegIFN and RBV significantly increased SVR12 in HCV genotype-1-infected treatment-naïve patients compared with PegIFN and RBV alone. While efficacy was similar for both doses of faldaprevir across all subgroups examined, the lower dose (120 mg) was better tolerated, specifically regarding GI events and photosensitivity. Since the completion of this study, faldaprevir development has been terminated for non-medical reasons in view of the fast progress in development of interferon-free regimens, and several all-oral direct-acting antiviral regimens have demonstrated high SVR12 rates with 12 weeks of treatment [37,38]. The results of the current study mark an important milestone in HCV therapeutics, demonstrating the commitment of patients and investigators to HCV research and attesting to the rapid pace at which the field has evolved.

Financial support

Boehringer Ingelheim Pharmaceuticals, GmbH & Co. KG.

Conflict of interest

PF is a member of advisory boards or review panels of Roche, Pfizer, Novartis, Vertex, Salix, Madaus Rottapharm, Tibotec, Boehringer Ingelheim, and Achillion. He has served as a speaker for Roche, Gilead, and Salix. He has also received grants or research support from Vertex and Madaus Rottapharm.

TA is a consultant for BMS, Boehringer Ingelheim, Roche, Merck-Schering Plough, Gilead, and Janssen.

GRF has received consultancy fees from Boehringer Ingelheim, BMS, Janssen, Gilead, Novartis, GSK, Regulus, Idenix, and Merck.

SZ has received consultancy fees from AbbVie, BMS, Boehringer Ingelheim, Gilead, Idenix, Janssen, Merck, Novartis, Presidio, Roche, Santaris, and Vertex.

CS has served on advisory boards for Abbott, Achillion, Boehringer Ingelheim, BMS, Janssen, Gilead, Merck, Novartis, Roche, and Vertex; was on speakers' bureaus for Abbott, Boehringer Ingelheim, BMS, Falk, Gilead, Janssen, Merck, Novartis, Roche, and Siemens; and has received research support from Abbott, Gilead, Janssen, Merck, Roche, and Siemens.

CM has served on advisory boards for BMS, Gilead, Janssen, and Merck; has received research grants from Astellas, Janssen, Merck, Novartis, and Roche; and has been an investigator for Novartis, Roche, Merck, Gilead, BMS, Boehringer Ingelheim, and Janssen.

FC has received consulting fees from Boehringer Ingelheim, Gilead, Janssen, Merck, and Roche; has received lecture fees from BMS, Gilead, Janssen, Merck, and Roche; and has received grant support from AbbVie, BMS, Boehringer Ingelheim, Janssen, and Merck.

JC has received consultant and lecture fees from Roche, Janssen, Gilead, and Merck.

J-FD is a member of advisory committees of Bayer, BMS, Gilead, Janssen, Jennerex, Merck, Novartis, and Roche. He has also received lecture fees from Bayer, Boehringer Ingelheim, Novartis, and Roche.

MB has served on advisory boards for Boehringer Ingelheim, Merck, Vertex, Janssen, Gilead, Abbott, GSK, and Roche; and has received lecture fees from Merck, Janssen, Boehringer Ingelheim, and Gilead.

KA has received grant support from BMS and Roche; and has received consultancy/lecturing fees from AbbVie, BMS, Gilead, Astex, Merck, Janssen, and Vertex.

DF has received consulting fees from AbbVie, BMS, Boehringer Ingelheim, Gilead, Janssen, Merck, and Roche.

MS has received consulting fees and speaker honoraries from Roche, Gilead, BMS, Merck, Boehringer Ingelheim, Janssen, and Falk.

SN received fees from Chugai Pharmaceutical, MSD, Dainippon Sumitomo Pharma, Ajinomoto Pharmaceuticals, and Otsuka Pharmaceutical.

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MO has received consulting fees from Boehringer Ingelheim and Gilead.

GK, MG, JS, A-MQ, and JOS are all employees of Boehringer Ingelheim Pharmaceuticals, Inc.

YD is an employee of Boehringer Ingelheim Pharmaceuticals GmbH and Co. KG.

DO, MM, LEM, and EZ have nothing to disclose.

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PF, TA, GRF, SZ, CS, CM, DO, MM, FC, LEM, JC, JFD, MB, KA, DF, MS, EZ, SN, MO, JOS, GK, YD, MG, JS, and AMQ contributed to the writing and review of this manuscript. PF, TA, GRF, SZ, CS, CM, DO, MM, FC, LEM, JC, JFD, MB, KA, DF, MS, EZ, SN, and MO were study investigators and contributed to recruitment of patients. PF, TA, GRF, SZ, CS, CM, DO, MM, FC, LEM, JC, JFD, MB, KA, DF, MS, EZ, SN, and MO contributed to data collection. JS and MG conducted statistical analyses. PF, TA, GRF, SZ, CS, CM, DO, MM, FC, LEM, JC, JFD, MB, KA, DF, MS, EZ, SN, MO, JOS, GK, YD, MG, JS, and AMQ contributed to the data interpretation. PF, JOS, GK, YD, MG, JS, and AMQ contributed to the study design.

Acknowledgements

This study was funded by Boehringer Ingelheim Pharmaceuticals GmbH & Co KG. The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development and have approved the final version. Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Katharine Howe of Adelphi Communications Ltd. and Andrew Brooks of Choice Healthcare Solutions, during the preparation of this manuscript.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2014.12.024.

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